Application no.: 09/942,310 Docket no.: SGL-2019-UT

REMARKS

Claims 17-31 are pending herein and claims 17 and 18 are amended. Basis for the amendments is in the specification throughout (e.g., page 5, lines 1-7) and no prohibited new matter has been added.

Applicants acknowledge the withdrawal of rejections under 35 U.S.C. §112, second paragraph, and under 35 U.S.C. §102. Applicants respectfully request reconsideration of the rejections set forth in the recent Office action in view of the amendments to claims 17 and 18 and the remarks hereafter.

The Office deemed the species election requirement proper and indicated it is not currently examining claims 20-26. Applicants have not cancelled claims 20-26 because they are generic to claims 17 and 18. The Applicants expect the Office will examine subject matter of claims 20-26 upon determining amended claims 17 and 18 are allowable.

The pending claims are rejected on two grounds by the Office: that there is an alleged lack of written description and an alleged lack of enablement. Applicants respectfully traverse these rejections for the reasons presented hereafter.

Rejection for Alleged Lack of Written Description

The Office rejected claims 17 and 27-32 for alleged lack of written description under 35 U.S.C. §112, first paragraph. The Office cited *The Regents of the University of California v. Eli Lilly*, 43 USPQ.2d 1398 (Fed. Cir. 1997) in support of the rejection (hereafter "*Lilly*"). In *Lilly*, the patentee described the nucleotide sequence for one species of cDNA that encoded rat insulin and the Office issued genus claims directed to DNA encoding vertebrate and mammalian insulin. The Court of Appeals for the Federal Circuit in *Lilly* concluded the following:

> It has been consistently held that the naming of one member of...a group is not, in itself, a proper basis for a claim to the entire group. However, it may not be necessary to enumerate a plurality of species if a genus is sufficiently identified in an application by 'other appropriate language.' We will not speculate in what other ways a broad genus of genetic material may be properly described, but it is clear to us, as it was to the district court, that the claimed genera of vertebrate and mammal

> cDNA are not described by the general language of the '525 patent's written description supported only by the specific nucleotide sequence of rat insulin (emphasis added).

Lilly at 1406. Thus, the *Lilly* decision pertains to the issue of whether a single species provides an adequate written description for a cDNA composition genus. As to the issue of what description is required to support a genus, Applicants are not required to disclose every species encompassed by a genus, and the description of a genus can be achieved by recitation of a representative number of species.

The subject matter of the pending claims and the description provided by the present specification are distinct from those of *Lilly*. Claim 17 and its dependent claims are directed to a method for predicting the capacity to metabolize a substrate of a CYP2D6 enzyme by analysis of a haplotype pair in a CYP2D6 5' flanking region. The present specification defines a haplotype as a collection of nucleotides at polymorphic sites grouped on a nucleic acid strand (e.g., page 9, lines 23-26). Addition of the term "haplotype" to claim 17 by amendment therefore is not narrowing because it clarifies subject matter already claimed (*i.e.*, nucleotides at three or more polymorphic sites on one strand of a nucleic acid).

In contrast to the fact pattern in *Lilly*, the present specification describes not one haplotype combination, but a group of several haplotype combinations useful for performing the claimed methods. For example, eight (8) haplotype combinations are disclosed in claim 18. Thus, the Applicants disclosed several haplotype combinations for predicting metabolic capacity of a CYP2D6 substrate, demonstrating that they had possession of the methods claimed.

Further, this group of disclosed haplotype combinations is a representative number of species for the genus claimed. Haplotypes in this group comprise polymorphic sites dispersed across the majority of the 5' flanking region, as shown in Figure 2. Figure 2 depicts a human CYP2D6 5' flanking region sequence and polymorphic sites in the group of haplotype combinations disclosed are highlighted by bold text. The polymorphic sites of these haplotype combinations span the 5' flanking region and therefore provide representation of polymorphic sites across its length. Thus, the specification describes a representative number of haplotype combination species for predicting metabolic capacity of a CYP2D6 substrate, evidence that Applicants were in possession of the claimed methods.

The language of claim 17 also provides a clear description of the haplotype genus. While the Court in *Lilly* focused on nucleotide sequence information, since the claims under analysis were directed to cDNA compositions, it also left open other frameworks for defining genetic information (see above). Here the claims are directed to methods of using haplotypes, not cDNA compositions, and therefore linear sequence information is not a pertinent description. Rather, the term a haplotype "comprising three or more polymorphic sites in a CYP2D6 5' flanking region" structurally defines the genus of claim 17. The 5' flanking region is a defined track of nucleotides (e.g., Figure 2) and three or more polymorphic sites are dispersed within the defined track. The person of ordinary skill in the art therefore can understand the structural limits of the region from which polymorphic sites in a haplotype are selected, and as described above, the specification provides a representative selection of polymorphic sites for the haplotype genus. Thus, Applicants had possession of the claimed methods and the specification provides a written description for the full scope of the claims.

In view of this written description, Applicants respectfully submit the grounds for the rejection in the Office action are not applicable to amended claim 17 and its dependent claims. The Office's position that the structure of one allele does not provide an adequate written description for the claims (end of page 4 and beginning of page 5 of the action), is not applicable. Eight (8) haplotype combination species are provided, thereby providing a representative number of species in support of the genus of claim 17. The statement that "no common structural attributes identify the members of the genus" (page 4 of the action) also is not applicable to the pending claims. The haplotypes are composed of polymorphic sites selected along the 5' flanking region sequence, this sequence is defined (e.g., Figure 2), and haplotypes are constructed from a representative number of polymorphic sites across the sequence. Thus, the specification provides a clear structural definition of the haplotypes claimed.

Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §112, first paragraph for alleged lack of written description since the specification evidences Applicants had possession of the claimed methods at the time of filing.

Rejection for Alleged Lack of Enablement

The Office rejected claims 17-19 and 27-32 for alleged lack of enablement under 35 U.S.C. §112, first paragraph. The Office offered three (3) rationale in support of its position that the scope

of the previously pending claims allegedly was not enabled by the specification. Each of these rationale are addressed hereafter with respect to the amended claims.

1. Capacity Determinations in Caucasians are Enabled

Claim 17, which was directed to determining the capacity for metabolizing a CYP2D6 substrate in a human, was rejected by the Office for alleged lack of enablement. The Office's main positions were the field allegedly was unpredictable (pages 7 and 8 of the action), and the frequency of a given marker can vary in different racial populations (page 9 of the action).

Applicants respectfully submit the rejection is inapplicable to the amended claims. Claim 17 and its dependent claims are directed to methods for predicting a Caucasian's capacity to metabolize a substrate of a CYP2D6 enzyme. This amendment is introduced for the purpose of expediting prosecution and is in no way an admission that broader populations are not enabled by the specification.

The claimed methods are in accord with the enablement requirements articulated in *In re Wands* and *Ex Parte Foreman*. Specifically, the present specification provides a working example of the claimed methods, in which haplotypes defined by nucleotides at three polymorphic positions in the CYP2D6 5' flanking region were utilized to predict metabolic capacity in a Swedish Caucasian population. Results of the example are summarized in Table 13 on page 26. The specification also provides specific guidance with regard to the populations studied, specific polymorphic positions for haplotype analysis, methodology utilized to determine nucleotides at specific positions for the haplotype analysis, and applying haplotype information for predicting metabolic capacity (e.g., Example 2 and Example 3).

Thus, the level of guidance and specific examples in the specification teach application of the claimed methods to Caucasians. A document cited by the Office on page 9 of the action, Ozawa *et al., Drug Metab. Pharmacokin. 19(2)*: 83-95 (2004), provides evidence that the person of ordinary skill in the art considered studies of Swedish populations as generally indicative of Caucasian population traits. Ozawa *et al.* shows in Figure 1 that debrisoquine hydroxylation metabolic profiles from Swedish and Spanish populations are similar, and are distinct from profiles of populations from China and Africa. Ozawa *et al.* also generally group Caucasians together throughout the document and compare the population to Chinese and African populations. Thus, the specific examples in the specification for Swedish populations are representative of Caucasians

in general and Applicants are not aware of evidence provided by the Office contrary to this position. If desired, a person of ordinary skill in the art can extend these methods taught in the specification to individuals in other Caucasian populations in a routine manner, especially in view of the high level of skill in the art recognized by the Office (page 12 of the action). The Court of Appeals for the Federal Circuit has deemed a large quantity of experimentation is acceptable when it is routine, (e.g., *In re Wands*, 8 USPQ.2d 1400, 1404 (Fed. Cir. 1988)). Thus, application of the methods taught in the specification to other populations is not undue.

The specification enables metabolic capacity determinations in Caucasians and therefore enables the full scope of claim 17 and its dependent claims.

2. Debrisoquine is Representative of Other Substrates

The Office alleges the term "capacity to metabolize a substrate of a CYP2D6 enzyme" is not enabled by the specification as the working examples describe methods for predicting metabolic capacity for one drug, debrisoquine, and not multiple drugs. Applicants respectfully submit debrisoquine is a model drug that represents CYP2D6 metabolic properties of many other drugs. The specification states on page 2, line 17 that debrisoquine is a "marker drug" and documents in the literature refer to the drug as a "probe." Kimura *et al., Am. J. Hum. Genet. 45*: 889-904 (1989) explain debrisoquine is "inefficiently metabolized by a significant number of individuals" and that this "lack of metabolism resulted in exaggerated response during clinical administration of the drug" on page 890. This exaggerated response provides a level of sensitivity useful for determining the effect of CYP2D6 polymorphisms, which is the reason why the drug is utilized as a probe for CYP2D6 activity. Kimura *et al.* also explain CYP2D6 genetic defects were discovered by assessing metabolic processing of debrisoquine, and that "[n]umerous other drugs and chemicals have been shown to be subjected to this genetic defect." Thus, Kimura demonstrates the usefulness of debrisoquine as a representative drug for CYP2D6 assessments.

Other evidence supports the use of debrisoquine as a representative drug for CYP2D6 assessments. Evans *et al., Pharmacogentics 5*: 64-71 (1995) state drug metabolism results with dextromethorphan were "very similar" to previous figures obtained using debrisoquine on page 68. Bertilsson, *Clinical Pharmacokinet. 29(3)*: 192-209 (1995) states poor "metabolizers (PMs) of debrisoquine were shown to be PMs of sparteine as well" in Caucasians on page 194. On page 199, Bertilsson shows metabolism of debrisoquine correlated with metabolism of the neuroleptic drug

haloperidol, and on page 198 shows metabolism of the antidepressant desipramine was determined based upon debrisoquine metabolism results.

Accordingly, debrisoquine is regarded in the art as a model drug representative of the metabolic properties of other drugs for CYP2D6 assessments. The working examples in the present specification using debrisoquine therefore enable the full scope of the claimed methods.

3. The Claimed Haplotype Analysis is Enabled

The Office alleges detecting any three or more polymorphic sites in a CYP2D6 flanking region is not enabled by the specification. Applicants respectfully submit the specification enables the amended claims. The specification provides a working example, Example 3, of the claimed methods for determining a metabolic capacity of a CYP2D6 enzyme from a haplotype on each chromosome comprising three or more polymorphic sites in the flanking region of the CYP2D6 gene. Table 13 shows that metabolic ratio can be predicted effectively when a haplotype from each chromosome is determined, and that three polymorphic sites in the haplotype are sufficient for making the determination across the entire range of available metabolic ratios. The polymorphic sites represented in Table 13 are at positions -1496, -1338 and -590. The specification on page 26, lines 1-6, provides additional haplotype combinations of three polymorphic positions, as it teaches (1) position -1338 can be replaced with position -912 and (2) position -590 can be replaced with position -652, and result in a method having the same resolving power as the haplotype combination shown in Table 13. The specification provides several additional haplotype combinations on page 5, lines 8-24, and a total of eight (8) haplotype combinations. Thus, the specification provides a working example and specific guidance that enable the claimed methods.

While it is possible other useful haplotype combinations may exist, the specification provides guidance for their selection. As noted above, the specification provides clear guidance for selecting study populations, specific polymorphic positions for haplotype analysis, methodology utilized to determine nucleotides at specific positions for the haplotype analysis, and applying haplotype information for predicting metabolic capacity (e.g., Example 2 and Example 3). If desired, a person of ordinary skill in the art can extend these teachings to other polymorphic sites and haplotype combinations in a routine manner, especially in view of the high level of skill in the art recognized by the Office (page 12 of the action). The Court of Appeals for the Federal Circuit has deemed a large quantity of experimentation is acceptable when it is routine, (e.g., *In re Wands*,

8 USPQ.2d 1400, 1404 (Fed. Cir. 1988)). Thus, application of the methods taught in the specification to other polymorphic sites and haplotype combinations is not undue.

Amended claim 17 specifies the metabolic capacity is determined from a haplotype on each chromosome, a haplotype pair, and therefore the position asserted in the first full paragraph on page 12 of the action is rendered moot. The discussion on page 11 of the action in connection with Raimundo *et al.*, however, is not clear to Applicants. Table 13 in the specification is directed to specific haplotype pairs, such as the H4/H4 pair. The CTG(A) haplotype discussed in Raimundo *et al.* is not present in the haplotype pairs in Table 13, and therefore is not pertinent. The CTG haplotype pair discussed in Raimundo *et al.* is for a single individual and it may not be statistically relevant. Results in Table 13 are more statistically relevant as multiple individuals fell into each haplotype pair category.

As the specification enables the full scope of the amended claims, Applicants respectfully request the Office withdraw its rejection under 35 U.S.C. §112, first paragraph, for alleged lack of enablement.

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CONCLUSIONS

Applicants respectfully submit that the claims pending herein are in condition for allowance, and they earnestly solicit an early notice to such effect. That said, should any issues or questions remain, the Examiner is encouraged to telephone the undersigned at (858) 623-9470 so that they may be promptly resolved.

In the unlikely event the transmittal letter is separated from this document and the Office determines that an extension and/or other relief is required, Applicants petition for any required relief, including extensions of time, and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account **503473**.

Respectfully submitted,

Dated: February 27, 2006 By: _____

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